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☐ 1. Document ID: US 6267957 B1

L7: Entry 1 of 24 File: USPT Jul 31, 2001

US-PAT-NO: 6267957
DOCUMENT-IDENTIFIER: US 6267957 B1

TITLE: Attaching agents to tissue with transglutaminase and a transglutaminase substrate

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Green; Howard	Brookline	MA	02146	
Corey; George D.	Newton	MA	02165	
Compton; Bruce J.	Lexington	MA	02173	
Dijan; Philippe	75015 Paris			FRX

US-CL-CURRENT: 424/94.5; 424/401, 424/59, 424/94.63, 435/16, 435/177, 435/193, 514/2, 530/402, 530/812

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6242010 B1

L7: Entry 2 of 24 File: USPT Jun 5, 2001

US-PAT-NO: 6242010
DOCUMENT-IDENTIFIER: US 6242010 B1

TITLE: Synergistic antioxidant compositions in management of hemorrhoids and other ano-rectal inflammatory conditions

DATE-ISSUED: June 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hersh; Theodore	Atlanta	GA		

US-CL-CURRENT: 424/702; 424/400, 424/729, 424/94.1, 424/DIG.15, 514/562, 514/882, 514/937, 514/944, 514/966, 514/969

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6204248 B1

L7: Entry 3 of 24 File: USPT Mar 20, 2001

US-PAT-NO: 6204248
DOCUMENT-IDENTIFIER: US 6204248 B1

TITLE: Pharmaceutical preparations of glutathione and methods of administration thereof

DATE-ISSUED: March 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Demopoulos; Harry B.	Scarsdale	NY		
Seligman; Myron L.	Fairfield	CT		

US-CL-CURRENT: 514/21; 514/18

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6159500 A

L7: Entry 4 of 24 File: USPT Dec 12, 2000

US-PAT-NO: 6159500
DOCUMENT-IDENTIFIER: US 6159500 A

TITLE: Pharmaceutical preparations of glutathione and methods of administration thereof

DATE-ISSUED: December 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Demopoulos; Harry B.	Scarsdale	NY		
Seligman; Myron L.	Pleasantville	NY		

US-CL-CURRENT: 424/456; 424/451, 424/452, 424/484, 514/18, 514/474, 514/824, 514/851, 514/866, 514/879, 514/894, 514/912 , 514/913, 514/931, 514/934, 514/970

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6139847 A

L7: Entry 5 of 24 File: USPT Oct 31, 2000

.US-PAT-NO: 6139847
DOCUMENT-IDENTIFIER: US 6139847 A

TITLE: Combined use of angiotensin inhibitors and nitric oxide stimulators to treat fibrosis

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chobanian; Aram	Natick	MA		
Brecher; Peter	West Newton	MA		

US-CL-CURRENT: 424/400; 514/310

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 6127356 A

L7: Entry 6 of 24 File: USPT Oct 3, 2000

US-PAT-NO: 6127356
DOCUMENT-IDENTIFIER: US 6127356 A

TITLE: Oxidant scavengers

DATE-ISSUED: October 3, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Crapo; James D.	Durham	NC		
Fridovich; Irwin	Durham	NC		
Oury; Tim	Durham	NC		
Day; Brian J.	Durham	NC		
Folz; Rodney J.	Durham	NC		
Freeman; Bruce A.	Birmingham	AL		
Trova; Michael P.	Schenectady	NY		
Batinic-Haberle; Ines	Durham	NC		

US-CL-CURRENT: 514/185; 252/399, 252/400.23, 435/189, 435/252.3, 435/320.1, 540/145

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 6080877 A

L7: Entry 7 of 24 File: USPT Jun 27, 2000

US-PAT-NO: 6080877
DOCUMENT-IDENTIFIER: US 6080877 A

TITLE: Taxanes

DATE-ISSUED: June 27, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Swindell; Charles S.	Merion	PA		
Shashoua; Victor E.	Brookline	MA		
Bradley; Matthews O.	Laytonsville	MD		
Webb; Nigel L.	Bryn Mawr	PA		

US-CL-CURRENT: 549/510; 549/511

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 8. Document ID: US 6071962 A

L7: Entry 8 of 24 File: USPT Jun 6, 2000

US-PAT-NO: 6071962
DOCUMENT-IDENTIFIER: US 6071962 A

TITLE: Oxa acids and related compounds for treating skin conditions

DATE-ISSUED: June 6, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ptchelintsev; Dmitri	Mahwah	NJ		
Scancarella; Neil D.	Wyckoff	NJ		
Kalafsky; Robert	Ogdensburg	NJ		

US-CL-CURRENT: 514/558; 514/513, 514/559, 514/560

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 9. Document ID: US 6048886 A

L7: Entry 9 of 24 File: USPT Apr 11, 2000

US-PAT-NO: 6048886
DOCUMENT-IDENTIFIER: US 6048886 A

TITLE: Compositions and delivery systems for the topical treatment of psoriasis and other conditions of the skin

DATE-ISSUED: April 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Neigut; Stanley	Plymouth Meeting	PA	19462	

US-CL-CURRENT: 514/412

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 10. Document ID: US 6013646 A

L7: Entry 10 of 24 File: USPT Jan 11, 2000

US-PAT-NO: 6013646
DOCUMENT-IDENTIFIER: US 6013646 A

TITLE: Indolocarbazole derivatives useful for the treatment of neurodegenerative diseases and cancer

DATE-ISSUED: January 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roder; Hanno	Ratingen			DEX
Lowinger; Timothy B.	Nishinomiya			JPX
Brittelli; David R.	Branford	CT		
VanZandt; Michael C.	Guilford	CT		

US-CL-CURRENT: 514/219; 540/556

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 11. Document ID: US 6004798 A

L7: Entry 11 of 24 File: USPT Dec 21, 1999

US-PAT-NO: 6004798
DOCUMENT-IDENTIFIER: US 6004798 A

TITLE: Retroviral envelopes having modified hypervariable polyproline regions

DATE-ISSUED: December 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Anderson; W. French	San Marino	CA		
Wu; Bonnie Weimin	Pasadena	CA		

US-CL-CURRENT: 435/235.1; 435/320.1, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 12. Document ID: US 5994339 A

L7: Entry 12 of 24 File: USPT Nov 30, 1999

US-PAT-NO: 5994339
DOCUMENT-IDENTIFIER: US 5994339 A

TITLE: Oxidant scavengers

DATE-ISSUED: November 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Crapo; James D.	Durham	NC		
Fridovich; Irwin	Durham	NC		
Oury; Tim	Durham	NC		
Day; Brian J.	Durham	NC		
Folz; Rodney J.	Durham	NC		
Freeman; Bruce A.	Birmingham	AL		

US-CL-CURRENT: 514/185; 252/399, 252/400.23, 435/189, 435/252.3, 435/320.1, 540/145

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 13. Document ID: US 5922773 A

L7: Entry 13 of 24 File: USPT Jul 13, 1999

US-PAT-NO: 5922773
DOCUMENT-IDENTIFIER: US 5922773 A

TITLE: Glaucoma treatment

DATE-ISSUED: July 13, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lipton; Stuart A.	Newton	MA		
Dreyer; Evan B.	Newton	MA		

US-CL-CURRENT: 514/649; 514/912, 514/913

Full | Title | Citation | Front | Review | Classification | Date | Reference KWMC | Draw. Desc | Image

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☐ 14. Document ID: US 5922346 A

L7: Entry 14 of 24 File: USPT Jul 13, 1999

US-PAT-NO: 5922346
DOCUMENT-IDENTIFIER: US 5922346 A

TITLE: Antioxidant preparation

DATE-ISSUED: July 13, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hersh; Theodore	Atlanta	GA		

US-CL-CURRENT: 424/439; 424/440, 424/441, 424/464, 424/702, 514/2, 514/904

Full | Title | Citation | Front | Review | Classification | Date | Reference KWMC | Draw. Desc | Image

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☐ 15. Document ID: US 5919815 A

L7: Entry 15 of 24 File: USPT Jul 6, 1999

US-PAT-NO: 5919815
DOCUMENT-IDENTIFIER: US 5919815 A

TITLE: Taxane compounds and compositions

DATE-ISSUED: July 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bradley; Matthews O.	Laytonville	MD		
Shashoua; Victor E.	Brookline	MA		
Swindell; Charles S.	Merion	PA		
Webb; Nigel L.	Bryn Mawr	PA		

US-CL-CURRENT: 514/449; 549/510

Full | Title | Citation | Front | Review | Classification | Date | Reference KWMC | Draw Desc | Image

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☐ 16. Document ID: US 5910316 A

L7: Entry 16 of 24 File: USPT Jun 8, 1999

US-PAT-NO: 5910316
DOCUMENT-IDENTIFIER: US 5910316 A

TITLE: Use of nitric oxide-releasing agents to treat impotency

DATE-ISSUED: June 8, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Keefer; Larry K.	Bethesda	MD		
Saavedra; Joseph E.	Thurmont	MD		
Doherty; Paul C.	Cupertino	CA		
Hanamoto; Mark S.	Belmont	CA		
Place; Virgil A.	Kawaihae	HI		

US-CL-CURRENT: 424/433; 514/963, 600/38

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 17. Document ID: US 5906811 A

L7: Entry 17 of 24 File: USPT May 25, 1999

US-PAT-NO: 5906811
DOCUMENT-IDENTIFIER: US 5906811 A

TITLE: Intra-oral antioxidant preparations

DATE-ISSUED: May 25, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hersh; Theodore	Atlanta	GA		

US-CL-CURRENT: 424/54; 424/49, 604/58

Full | Title | Citation | Front | Review | Classification | Date | Reference KWMC | Draw Desc | Image

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☐ 18. Document ID: US 5847003 A

L7: Entry 18 of 24 File: USPT Dec 8, 1998

US-PAT-NO: 5847003
DOCUMENT-IDENTIFIER: US 5847003 A

TITLE: Oxa acids and related compounds for treating skin conditions

DATE-ISSUED: December 8, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ptchelintsev; Dmitri	Mahwah	NJ		
Scancarella; Neil	Wyckoff	NJ		
Kalafsky; Robert	Ogdensburg	NJ		

US-CL-CURRENT: 514/532; 514/546, 514/549, 514/558, 514/559, 514/560

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 19. Document ID: US 5834513 A

L7: Entry 19 of 24 File: USPT Nov 10, 1998

US-PAT-NO: 5834513
DOCUMENT-IDENTIFIER: US 5834513 A

TITLE: Oxa diacids and related compounds for treating skin conditions

DATE-ISSUED: November 10, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ptchelintsev; Dmitri	Mahwah	NJ		
Scancarella; Neil	Wyckoff	NJ		
Kalafsky; Robert	Ogdensburg	NJ		

US-CL-CURRENT: 514/561; 514/564, 514/566, 514/574

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 20. Document ID: US 5827886 A

L7: Entry 20 of 24 File: USPT Oct 27, 1998

US-PAT-NO: 5827886
DOCUMENT-IDENTIFIER: US 5827886 A

TITLE: Composition for relief of arthritis-induced symptoms

DATE-ISSUED: October 27, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hersh; Theodore	Atlanta	GA		

US-CL-CURRENT: 514/562; 424/702, 514/162, 514/165, 514/171, 514/474, 514/561, 514/627

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 21. Document ID: US 5795909 A

L7: Entry 21 of 24 File: USPT Aug 18, 1998

US-PAT-NO: 5795909
DOCUMENT-IDENTIFIER: US 5795909 A

TITLE: DHA-pharmaceutical agent conjugates of taxanes

DATE-ISSUED: August 18, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shashoua; Victor E.	Brookline	MA		
Swindell; Charles S.	Merion	PA		
Webb; Nigel L.	Bryn Mawr	PA		
Bradley; Matthews O.	Laytonsville	MD		

US-CL-CURRENT: 514/449; 514/549

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 22. Document ID: US 5691423 A

L7: Entry 22 of 24 File: USPT Nov 25, 1997

US-PAT-NO: 5691423
DOCUMENT-IDENTIFIER: US 5691423 A

TITLE: Polysaccharide-bound nitric oxide-nucleophile adducts

DATE-ISSUED: November 25, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Smith; Daniel J.	Stow	OH		
Chakravarthy; Debashish	Garrettsville	OH		
Keefer; Larry K.	Bethesda	MD		

US-CL-CURRENT: 525/377; 424/499, 424/78.17, 536/18.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 23. Document ID: US 5645839 A

L7: Entry 23 of 24 File: USPT Jul 8, 1997

US-PAT-NO: 5645839
DOCUMENT-IDENTIFIER: US 5645839 A

TITLE: Combined use of angiotensin inhibitors and nitric oxide stimulators to treat fibrosis

DATE-ISSUED: July 8, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chobanian; Aram	Natick	MA		
Brecher; Peter	West Newton	MA		

US-CL-CURRENT: 424/400; 424/43, 424/451, 424/464, 424/474, 424/489, 514/310

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 24. Document ID: US 5597809 A

L7: Entry 24 of 24 File: USPT Jan 28, 1997

US-PAT-NO: 5597809
DOCUMENT-IDENTIFIER: US 5597809 A

TITLE: Treatment of optic neuritis

DATE-ISSUED: January 28, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dreyer; Evan B.	Chestnut Hill	MA		

US-CL-CURRENT: 514/34; 514/145, 514/148, 514/224.8, 514/231.2, 514/233.2, 514/256, 514/260, 514/277, 514/278, 514/299, 514/312, 514/314, 514/317, 514/345, 514/469, 514/492, 514/493, 514/498, 514/501, 514/504, 514/530, 514/601, 514/602, 514/608, 514/613, 514/616, 514/646, 514/647, 514/662, 514/664, 514/665, 514/706, 514/707, 514/724, 514/731, 514/734, 514/744, 514/745, 514/757, 514/759, 514/764, 514/912, 514/913, 514/914, 514/915

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USPT,JPAB,EPAB,DWPI,TDBD	(nitric adj1 oxide) same antioxidant$	137	L4
USPT,JPAB,EPAB,DWPI,TDBD	l2 and ascorb$	3	L3
USPT,JPAB,EPAB,DWPI,TDBD	(sexual adj1 dysfunction) same topical$	33	L2
USPT,JPAB,EPAB,DWPI,TDBD	(sexual adj1 dysfunction) same antioxidant$	1	L1

L7: Entry 2 of 24 File: USPT Jun 5, 2001

DOCUMENT-IDENTIFIER: US 6242010 B1
TITLE: Synergistic antioxidant compositions in management of hemorrhoids and other ano-rectal inflammatory conditions

ABPL:
Compositions for remediating ano-rectal inflammatory processes, hemorrhoidal syndromes and ano-rectal wounds. The composition includes the synergistic combination of reduced glutathione and selenium as a selenoamino acid in a suitable carrier for topical applications.

BSPR:
The present invention deals with compositions for ano-rectal inflammatory processes, hemorrhoidal syndromes, pruritus ani and ano-rectal wounds comprising a complex of synergistic antioxidants, including enzymatic co-factors, thiol and selenium compounds, zinc salts and cellular growth factors to decrease the local inflammatory response, abolish symptoms, and to promote wound healing and surgical repairs, such as post-hemorrhoidectomies, fistulectomies, and fissurectomies. These active ingredients will be administered using topical ano-genital and intra-rectal preparations, most particularly, ointments, salves, lotions, creams, patches, aerosols, sprays and others and as suppositories and foams for internal hemorrhoids and rectal inflammatory conditions so that the antioxidants neutralize and scavenge the free radicals generated in ano-rectal diseases and local wounds thereby reducing the pain, inflammation, swelling, itching, and tenderness in these anatomical parts, and together with other optional ingredients promote repair and healing.

BSPR:
Other causes of ano-rectal inflammation are sexually transmitted diseases and perianal infections and abscesses. The later often originate from a suppurative cryptitis, or from a fissure. Fistula-in-ano may result from a perianal abscess and is a chronic, indolent and painful condition. Inflammation is most prominent and requires antibiotics and drainage with local care including topical analgesics. The present antioxidant preparations would be an important adjunct in the symptomatic and reparative management of these ano-rectal inflammations.

BSPR:
There are a number of patents which have been issued for compositions and methods of treating hemorrhoids and related ano-rectal wounds. Topical formulations not only treat hemorrhoidal pain but also sphincter spasm and related symptoms. Gallina in U.S. Pat. No. 5,234,914 dated Aug. 10, 1993, taught a method of applying to ano-rectal tissues and to hemorrhoids a composition which included hyaluronic acid or its salts in amounts ranging from 0.1 to 10% by weight, in acceptable carriers. The uses of hyaluronic acid included its anti-inflammatory and wound healing properties for ano-rectal conditions and diseases,

BSPR:
U.S. Pat. No. 4,761,285, dated Aug. 2, 1988, taught various compositions for the relief of hemorrhoidal symptoms and the treatment of hemorrhoids. It taught a preparation comprising leptandra's culver root, chick peas, and grape seeds. The latter are now known to contain proanthocynidins, antioxidants which are also present in pine bark extracts. These investigators enhanced their topical preparation with honey, cinnamon and oils. Okumura and associates more recently

disclosed the use of prostaglandins in the therapy of hemorrhoids and wounds in U.S. Pat. No. 5,852,050 dated Dec. 22, 1998, which is herein incorporated by reference. Stable prostaglandins, as Geraprost, are used as oral or topical preparations because these prostaglandins improve peripheral blood circulation while inhibiting thrombus formation through a decrease in platelet aggregation.

BSPR:
In U.S. Pat. No. 4,613,498 dated Sep. 23, 1986, Crosby disclosed an external hemorrhoid medication as a petroleum jelly ointment. The reference taught a powdered mixture of alum, quinine sulfate and aspirin be applied topically to the affected area. Anderson, in U.S. Pat. No. 4,162,866 dated Mar. 11, 1980, taught an anorectal medication comprising glycerides and fragments of the ripe berry of the plant solanum carolinense (horse nettle). The reference also included sulfur, ammonium alum and turpentine. Earlier, Urbin, in U.S. Pat. No. RE28,0 dated May 14, 1974 disclosed the use of oxidase enzymes to treat hemorrhoids, by destroying the amines formed by the fecal microflora in the colon.

BSPR:
U.S. Pat. No. 5,595,753, dated Jan. 21, 1997, taught the use of L-arginine for topical formulations for treating hemorrhoidal pain and sphincteric muscle spasm in gastrointestinal tract. Inflammation of the anal mucosa and hemorrhoids cause spasms of the internal anal sphincter with consequent ano-rectal pain. The pain associated with hemorrhoids is due primarily to the adjacent inflammatory reaction. Nitric oxide (NO) is a known modulator of sphincter tone, to which the amino acid L-arginine acts as a competitive inhibitor of compounds that block the action of NO production. Thus, L-arginine's use as taught in the '753 patent in topical preparations, alleviates anal pain by decreasing internal sphincter tone and thereby abolishing sphincter spasm. This amino acid does not participate as an antioxidant in the amelioration of the local inflammatory response, as proposed by the compositions of the present patent application.

BSPR:
Suppositories consisting of tissue respiratory factor as the active ingredient are known. Analgesic and anti-inflammatory compositions for topical applications were also disclosed by Reller and Kretschmar in U.S. Pat. No. 4,199,576, Apr. 22, 1980. The reference taught a number of salicylic acid derivatives as useful non-irritating topical anti-inflammatory agents which, like aspirin, are inhibitors of prostaglandin synthesis. Like the latter, histamine, serotonin, and the kinins are mediators of inflammation but with these the prostaglandins are continuously biosynthesized and released from the cells at the site of inflammation. Since prostaglandins have a longer effect in situ, it is suggested by the present invention that it is vital to decrease inflammation's free radical tissue damage with topical antioxidants plus the known anti-inflammatory agents like the salicylates, steroids and other derivatives so well known in the art of this industry.

BSPR:
There are many other over the counter ano-rectal products, but none contain the antioxidant complex of the present invention. They contain other topically beneficial ingredients for ano-rectal conditions, each with designated therapeutic goals, for example, vaso-constrictors and analgesics to decrease pain, itching, swelling, soreness or to diminish the size of the hemorrhoids or its bleeding complications. Some examples of these OTC products include americaine, balneol, calmol-y, cortex rectal itch ointment, diothane, epinephricaine, gentzy and tucks wipes, proctofoam, nupercainal, Vaseline, wyanoids, and many others. These all conform to Code of Federal Regulations 45-33576, dated May 22, 1980.

BSPR:
The composition includes the reduced form of glutathione with a selenium source as a co-factor of glutathione peroxidase as antioxidants. The composition may be topically applied as a lotion, cream, ointment, gel, spray or emulsion or by its inclusion into a suppository vehicle or foam together with further wound healing ingredients, anti-inflammatories and analgesics as discussed below.

BSPR:
Selenium functions as an anti-oxidant and by its role as a cofactor for glutathione peroxidase, a group of water soluble enzymes which also catalyze the destruction of both aqueous and membrane-bound hydroperoxides. In dietary selenium deficiency, these enzyme levels are markedly decreased resulting in severe free radical damage to the tissues so involved. The other related anti-oxidant systems cannot make up for depressed local activity of selenium and selenium dependent enzymes. Selenium deficiency also occurs after such injuries as burns and needs to be supplemented in these states. Thus, the importance of providing selenium in these topical anti-oxidant preparations, as well as ascertaining adequate dietary supplements. Indeed, recent epidemiologic studies have shown that supplemental selenium at a dose of 200 mcgm daily, may reduce both the incidence of and the mortality from carcinomas of various sites.

BSPR:
Selenium has also been shown to affect the immune system. Selenium supplementation as 70% selenomethione in patients with psoriasis with normal pretreatment selenium blood levels showed an increase in blood levels of 40% post treatment. A statistically significant increase in the number of CD4 +T-cells was noted in the reticular dermis of the psoriatic lesions. In other studies in human subjects, topical selenomethionine was investigated for its ability to reduce the degree of acute inflammatory damage to the skin by ultraviolet radiation. The effects demonstrated by topical selenomethionine in human volunteers on measurement of minimal erythema dose, suggests that the protection to ultraviolet irradiation by this compound is not simply a sunscreen effect. The selenomethionine is absorbed percutaneously and acts locally as a free radical scavenger.

BSPR:
Further, glutathione and selenium act synergistically in vivo as they are both constituents of the same enzymatic system. GSH serves as a specific donor substrate while selenium, provided from alimentary sources or locally from topically applied preparations of selenoamino acids, selenium yeast extracts or selenoamino acid chelates, provides the prosthetic group of GSH peroxiclase. The glutathione and selenium antioxidant functions are intrinsically related since by keeping a peroxidase in action. GSH and selenium contribute to the removal of the dismutation product of free oxygen radicals, namely, hydrogen peroxide. In a broad sense, GSH and selenium modulate free radical chains initiated or sustained by hydroperoxides. Thus, their synergistic value in these antioxidant topical compositions.

BSPR:
It is also contemplated that, as a further optional expedient that the present composition contain from approximately 0.01% to 10.0% Japanese green tea by weight based upon the weight of the other active ingredients. Chemically, extracts of Japanese green tea have been analyzed and characterized. Active ingredients include caffeine, theobromine, theophylline and xanthines which, together, have been shown to reduce irritation of the skin, including that caused by various alpha hydroxy acids and other ingredients in cosmetics, thus making green tea an important supplement to topical cosmetic and dermatological preparations. Green tea also contains potent polyphenols, catechin compounds which effectively act as antioxidant agents to scavenge for free radicals. The main catechin constituent of green tea is (-)epigallocatechingallate (EGCG). It has also been shown that EGCG inhibits hydrogen peroxide formation by human leukocytes, the first cell in the inflammatory cellular response to injury and infection. EGCG is of value to function synergistically as an exogenous antioxidant in these topical preparations with the active ingredients composed of endogenous antioxidants.

BSPR:
As a further optional expedient is the use of epidermal growth factor (EGF), an endogenous substance for the development and maintenance of the epidermis and dermis. EGF is a protein that catalyzes the cutaneous healing process by promoting epidermal and epithelial cells to divide and grow. It induces mitoses,

so that these tissues constantly produce and use EGF, particularly when these tissues are damaged, such as in inflammatory reactions and after surgery for healing. When applied topically, EGF generates and replaces epithelial cells. EGF also promotes synthesis of proteins, accumulation of collagen and formation of blood vessels. The antioxidants protect and repair damaged ano-rectal tissues from free radicals while the growth factors to be used in these combinations will promote cell renewal and thus ensue in repair of affected tissues.

DEPR:
A rectal cream can be prepared with the active ingredients described above. The cream has a base of stearic acid, cetyl alcohol, isopropyl palmitate, polyoxyl-40 stearate, propylene glycol, triethanolamine, sorbic acid (0.1%), lauryl sulfate and water. Hydrocortisone at 1.0% to 2.5% depending on the concentration desired, may be added, as "H-C" preparations commonly known in over the counter ano-rectal preparations or by prescription. Topical corticosteroids enhance the anti-inflammatory properties of the antioxidant complex and are also known to be anti-pruritic and vasoconstrictive agents.

DEPR:
Suppositories can be formulated with base ingredients such as waxes, oils, and fatty alcohols with characteristics of remaining in solid state at room temperatures and melting at body temperatures. The active ingredients of this invention with or without optional therapeutic ingredients, like hydrocortisone (1.0%), topical anesthetics like benzocaine (1.0 to 6.0%) or others as already listed may be prepared at appropriate pH values; for example pH5 liquid fatty alcohols, such as oleyl alcohol (range 45% to 65%) or solid higher fatty alcohols like cetyl or stearyl alcohol (30% to 50%). The base ingredients are well known in the art of this industry and some have been disclosed in U.S. Pat. Nos. 4,945,084 and 5,196,405 both by Packman and Oskman, the disclosures of which are incorporated by reference.

DEPR:
The active ingredients in creams, lotions, ointments, sprays, pads, patches, enemas, foams and suppositories and others may be delivered in novel delivery vehicles such as micro-encapsulation in liposomes or glycospheres. Other delivery technologies include microsponges or the substitute cell membrane (Completech .TM.) which entrap the active ingredients for both protection and for slower release. Rectal foams can be prepared as topical aerosol compositions, again, as are well known in this industry with the express purpose of delivering the antioxidant complex of this application to reduce free radical damage in this ano-rectal inflammatory conditions, including inflammatory bowel diseases (ulcerative colitis, Crohns colitis, radiation proctitis and others).

CLPR:
1. A method for ameliorating symptoms of hemorrhoids and other ano-rectal inflammation comprising topically applying to the rectum an amount of a composition of a topical carrier and a source of selenium and reduced glutathione in amounts effective to ameliorate said symptoms.

WEST

End of Result Set

☐ Generate Collection

L1: Entry 1 of 1 File: USPT Jan 26, 1999

DOCUMENT-IDENTIFIER: US 5863927 A
TITLE: Dextromethorphan and an oxidase inhibitor for treating intractable conditions

DEPR:
It was noted that a side-effect suffered by some of the male patients in earlier emotionality studies and the dermatitis studies described in Example 7 included instances of impotence. This impotence persisted until the patient stopped taking medication containing DM-quinidine. Therefore, DM-antioxidants containing medicaments are contemplated for the treatment of sexual dysfunctions including priapism or premature ejaculation.

DEPR:
These examples demonstrate that the combination of dextromethorphan and an antioxidant such as quinidine are effective at treating intractable disorders, including intractable coughing, chronic pain, dermatitis, tinnitus and sexual dysfunction. Although this invention has been described with reference to the presently preferred embodiments, it is understood that various modifications can be made without departing from the spirit of the invention. According, the invention is limited only by the following claims.

WEST

Generate Collection

Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 6291498 B1

L3: Entry 1 of 3 File: USPT Sep 18, 2001

US-PAT-NO: 6291498
DOCUMENT-IDENTIFIER: US 6291498 B1

TITLE: Method for optimizing pupil size using alpha antagonist

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Horn; Gerald	Deerfield	IL	60015	

US-CL-CURRENT: 514/385; 514/912

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6087362 A

L3: Entry 2 of 3 File: USPT Jul 11, 2000

US-PAT-NO: 6087362
DOCUMENT-IDENTIFIER: US 6087362 A

TITLE: Apomorphine and sildenafil composition

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
El-Rashidy; Ragab	Deerfield	IL		

US-CL-CURRENT: 514/252.16; 514/284

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 5908853 A

L3: Entry 3 of 3 File: USPT Jun 1, 1999

US-PAT-NO: 5908853
DOCUMENT-IDENTIFIER: US 5908853 A

TITLE: Compositions

DATE-ISSUED: June 1, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nahoum; Cesar Roberto Dias				

US-CL-CURRENT: 514/341; 514/929

Generate Collection

Terms	Documents
l2 and ascorb$	3

Display 30 Documents, starting with Document: 3

Display Format: CIT Change Format

WEST

Generate Collection

Search Results - Record(s) 1 through 30 of 33 returned.

☐ 1. Document ID: US 6294550 B1

L2: Entry 1 of 33 File: USPT Sep 25, 2001

US-PAT-NO: 6294550
DOCUMENT-IDENTIFIER: US 6294550 B1

TITLE: Treatment of female sexual dysfunction

DATE-ISSUED: September 25, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihee	HI		
Wilson; Leland F.	Menlo Park	CA		
Doherty, Jr.; Paul C.	Cupertino	CA		
Hanamoto; Mark S.	Belmont	CA		
Spivack; Alfred P.	Menlo Park	CA		
Gesundheit; Neil	Los Altos	CA		
Bennett; Sean R.	Denver	CO		

US-CL-CURRENT: 514/302

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6291498 B1

L2: Entry 2 of 33 File: USPT Sep 18, 2001

US-PAT-NO: 6291498
DOCUMENT-IDENTIFIER: US 6291498 B1

TITLE: Method for optimizing pupil size using alpha antagonist

DATE-ISSUED: September 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Horn; Gerald	Deerfield	IL	60015	

US-CL-CURRENT: 514/385; 514/912

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 3. Document ID: US 6284263 B1

L2: Entry 3 of 33 File: USPT Sep 4, 2001

US-PAT-NO: 6284263
DOCUMENT-IDENTIFIER: US 6284263 B1

TITLE: Buccal drug administration in the treatment of female sexual dysfunction

DATE-ISSUED: September 4, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihae	HI	96743	

US-CL-CURRENT: 424/435; 424/434, 424/464, 514/772.3

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

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☐ 4. Document ID: US 6277884 B1

L2: Entry 4 of 33 File: USPT Aug 21, 2001

US-PAT-NO: 6277884
DOCUMENT-IDENTIFIER: US 6277884 B1

TITLE: Treatment of sexual dysfunction with N-hydroxyguanidine compounds

DATE-ISSUED: August 21, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Tejada; Inigo Saenz	Madrid			ESX

US-CL-CURRENT: 514/565

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

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☐ 5. Document ID: US 6258373 B1

L2: Entry 5 of 33 File: USPT Jul 10, 2001

US-PAT-NO: 6258373
DOCUMENT-IDENTIFIER: US 6258373 B1

TITLE: Treatment of sexual dysfunction in certain patient groups

DATE-ISSUED: July 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cutler; Neal R.	Los Angeles	CA	90077	

US-CL-CURRENT: 424/434; 424/435

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 6. Document ID: US 6251436 B1

L2: Entry 6 of 33 File: USPT Jun 26, 2001

US-PAT-NO: 6251436
DOCUMENT-IDENTIFIER: US 6251436 B1

TITLE: Drug preparations for treating sexual dysfunction

DATE-ISSUED: June 26, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Drizen; Alan	Ontario			CAX
Rothbart; Peter	Ontario			CAX
Nath; Gary M.	Bethesda	MD		

US-CL-CURRENT: 424/488; 424/484, 424/486, 514/530, 514/54, 514/57, 514/777, 514/781, 514/929, 514/944, 536/53

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 7. Document ID: US 6241529 B1

L2: Entry 7 of 33 File: USPT Jun 5, 2001

US-PAT-NO: 6241529
DOCUMENT-IDENTIFIER: US 6241529 B1

TITLE: Method for facilitating transmucosal delivery of steroidal active agents

DATE-ISSUED: June 5, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihae	HI	96743	

US-CL-CURRENT: 424/434; 424/435, 514/772.3, 514/781

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

☐ 8. Document ID: US 6221379 B1

L2: Entry 8 of 33 File: USPT Apr 24, 2001

US-PAT-NO: 6221379
DOCUMENT-IDENTIFIER: US 6221379 B1

TITLE: Buccal drug administration in female hormone replacement therapy

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihae	HI	96743	

US-CL-CURRENT: 424/435

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 9. Document ID: US 6214849 B1

L2: Entry 9 of 33 File: USPT Apr 10, 2001

US-PAT-NO: 6214849
DOCUMENT-IDENTIFIER: US 6214849 B1

TITLE: Use of nicorandil in treatment of sexual dysfunction or for enhancement of sexual function in mammals including humans

DATE-ISSUED: April 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Saxena; Ajit	Uttar Pradesh	IN		
Bakhle; Dhananjay Sadashiv	Mumbai	IN		

US-CL-CURRENT: 514/355; 514/906

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 10. Document ID: US 6200593 B1

L2: Entry 10 of 33 File: USPT Mar 13, 2001

US-PAT-NO: 6200593
DOCUMENT-IDENTIFIER: US 6200593 B1

TITLE: Contraceptive method employing buccal delivery of steroidal active agents

DATE-ISSUED: March 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihae	HI	96743	

US-CL-CURRENT: 424/435; 424/434, 424/464, 514/772.3

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 11. Document ID: US 6193976 B1

L2: Entry 11 of 33 File: USPT Feb 27, 2001

US-PAT-NO: 6193976
DOCUMENT-IDENTIFIER: US 6193976 B1

TITLE: Hair restorer containing vetiver grass extract

DATE-ISSUED: February 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Porras; Sandra E.	San Diego	CA		
Jochamowitz; Francisco Grippa	Iquitos			PEX

US-CL-CURRENT: 424/750; 424/70.1, 424/74, 514/880

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 12. Document ID: US 6143757 A

L2: Entry 12 of 33 File: USPT Nov 7, 2000

US-PAT-NO: 6143757
DOCUMENT-IDENTIFIER: US 6143757 A

TITLE: Chemical compounds

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Daugan; Alain Claude-Marie	Marly le Roi Cedex			FRX
LaBaudiniere; Richard Frederick	Collegeville	PA		

US-CL-CURRENT: 514/285; 514/277, 514/279, 514/284, 514/287, 514/359

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 13. Document ID: US 6143746 A

L2: Entry 13 of 33 File: USPT Nov 7, 2000

US-PAT-NO: 6143746
DOCUMENT-IDENTIFIER: US 6143746 A

TITLE: Tetracyclic cyclic GMP-specific phosphodiesterase inhibitors, process of preparation and use

DATE-ISSUED: November 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Daugan; Alain Claude-Marie	Marly le Roi Cedex			FRX
Gellibert; Francoise	Marly le Roi Cedex			FRX

US-CL-CURRENT: 514/249; 514/250, 514/292

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

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☐ 14. Document ID: US 6132757 A

L2: Entry 14 of 33 File: USPT Oct 17, 2000

US-PAT-NO: 6132757
DOCUMENT-IDENTIFIER: US 6132757 A

TITLE: Treatment of sexual dysfunction in certain patient groups

DATE-ISSUED: October 17, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cutler; Neal R.	Los Angeles	CA	90077	

US-CL-CURRENT: 424/434; 424/435, 424/45

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

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☐ 15. Document ID: US 6117446 A

L2: Entry 15 of 33 File: USPT Sep 12, 2000

US-PAT-NO: 6117446
DOCUMENT-IDENTIFIER: US 6117446 A

TITLE: Drug dosage unit for buccal administration of steroidal active agents

DATE-ISSUED: September 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihae	HI	96743	

US-CL-CURRENT: 424/435; 424/434

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

☐ 16. Document ID: US 6087362 A

L2: Entry 16 of 33 File: USPT Jul 11, 2000

US-PAT-NO: 6087362
DOCUMENT-IDENTIFIER: US 6087362 A

TITLE: Apomorphine and sildenafil composition

DATE-ISSUED: July 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
El-Rashidy; Ragab	Deerfield	IL		

US-CL-CURRENT: 514/252.16; 514/284

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

☐ 17. Document ID: US 6043252 A

L2: Entry 17 of 33 File: USPT Mar 28, 2000

US-PAT-NO: 6043252
DOCUMENT-IDENTIFIER: US 6043252 A

TITLE: Carboline derivatives

DATE-ISSUED: March 28, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bombrun; Agnes	Paris			FRX

US-CL-CURRENT: 514/292; 546/85

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

☐ 18. Document ID: US 6036977 A

L2: Entry 18 of 33 File: USPT Mar 14, 2000

US-PAT-NO: 6036977
DOCUMENT-IDENTIFIER: US 6036977 A

TITLE: Drug preparations for treating sexual dysfunction

DATE-ISSUED: March 14, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Drizen; Alan	Ontario			CAX
Rothbart; Peter	Ontario			CAX
Nath; Gary M.	Bethesda	MD		

US-CL-CURRENT: 424/488; 424/484, 424/486, 514/530, 514/54, 514/777, 514/781, 514/929, 536/53

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

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☐ 19. Document ID: US 5908853 A

L2: Entry 19 of 33 File: USPT Jun 1, 1999

US-PAT-NO: 5908853
DOCUMENT-IDENTIFIER: US 5908853 A

TITLE: Compositions

DATE-ISSUED: June 1, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Nahoum; Cesar Roberto Dias				

US-CL-CURRENT: 514/341; 514/929

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw. Desc | Image

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☐ 20. Document ID: US 5877216 A

L2: Entry 20 of 33 File: USPT Mar 2, 1999

US-PAT-NO: 5877216
DOCUMENT-IDENTIFIER: US 5877216 A

TITLE: Treatment of female sexual dysfunction

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Place; Virgil A.	Kawaihae	HI		
Wilson; Leland F.	Menlo Park	CA		
Doherty, Jr.; Paul C.	Cupertino	CA		
Hanamoto; Mark S.	Belmont	CA		
Spivack; Alfred P.	Menlo Park	CA		
Gesundheit; Neil	Los Altos	CA		
Bennett; Sean R.	Denver	CO		

US-CL-CURRENT: 514/573

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 21. Document ID: WO 9922731 A1

L2: Entry 21 of 33 File: EPAB May 14, 1999

PUB-NO: WO009922731A1
DOCUMENT-IDENTIFIER: WO 9922731 A1
TITLE: METHOD AND COMPOSITION FOR TREATMENT OF SEXUAL DYSFUNCTION

PUBN-DATE: May 14, 1999

INVENTOR-INFORMATION:

NAME	COUNTRY
VAISMAN, JAKOV	AU

INT-CL (IPC): A61K 31/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 22. Document ID: KR 2001009489 A

L2: Entry 22 of 33 File: DWPI Feb 5, 2001

DERWENT-ACC-NO: 2001-473602
DERWENT-WEEK: 200151
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TITLE: Liquid-type topical therapeutic agent for male sexual dysfunction

INVENTOR: KIM, C R

PRIORITY-DATA: 1999KR-0027871 (July 10, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 2001009489 A	February 5, 2001		001	A61K035/78

INT-CL (IPC): A61K 35/78

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 23. Document ID: AU 9939891 A, WO 200069469 A1

L2: Entry 23 of 33 File: DWPI Dec 5, 2000

DERWENT-ACC-NO: 2001-049791
DERWENT-WEEK: 200113
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TITLE: Topical compositions containing prostaglandin E1 are useful for treating female sexual dysfunction, peripheral vascular disease, male erectile dysfunction and for enhancing female sexual responsiveness

INVENTOR: BUYUKTIMKIN, N; BUYUKTIMKIN, S ; YEAGER, J L

PRIORITY-DATA: 1999WO-US10596 (May 13, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9939891 A	December 5, 2000		000	A61K047/00
WO 200069469 A1	November 23, 2000	E	032	A61K047/00

INT-CL (IPC): A61K 47/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 24. Document ID: AU 200023586 A, WO 200033825 A2

L2: Entry 24 of 33 File: DWPI Jun 26, 2000

DERWENT-ACC-NO: 2000-423200
DERWENT-WEEK: 200045
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TITLE: Compositions suitable for topical application of female sexual arousal disorder comprise vasoactive agent, polymer thickener, lipophilic component, penetration enhancer and buffer system

INVENTOR: BUYUKTIMKIN, N; BUYUKTIMKIN, S ; YEAGER, J L

PRIORITY-DATA: 1998US-0208965 (December 10, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200023586 A	June 26, 2000		000	A61K031/00
WO 200033825 A2	June 15, 2000	E	063	A61K031/00

INT-CL (IPC): A61K 31/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 25. Document ID: US 2001022975 A1, WO 200013664 A1, AU 9958129 A, EP 1112061 A1, US 6251436 B1

L2: Entry 25 of 33 File: DWPI Sep 20, 2001

DERWENT-ACC-NO: 2000-256833
DERWENT-WEEK: 200156
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TITLE: Treating sexual dysfunction comprises topically applying vasodilating drug in gelled polymer matrix dispersed in liquid medium

INVENTOR: DRIZEN, A; NATH, G M ; ROTHBART, P

PRIORITY-DATA: 1998US-0148986 (September 8, 1998), 1995US-0536750 (September 29, 1995), 1997US-0796578 (February 6, 1997), 1997US-0825121 (March 28, 1997), 1998US-0048335 (March 26, 1998), 2001US-0854509 (May 15, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 2001022975 A1	September 20, 2001		000	A61K009/14
WO 200013664 A1	March 16, 2000	E	073	A61K009/00
AU 9958129 A	March 27, 2000		000	A61K009/00
EP 1112061 A1	July 4, 2001	E	000	A61K009/00
US 6251436 B1	June 26, 2001		000	A61K009/14

INT-CL (IPC): A61K 9/00; A61K 9/14; A61K 31/557; A61K 47/36

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

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☐ 26. Document ID: US 6036977 A

L2: Entry 26 of 33 File: DWPI Mar 14, 2000

DERWENT-ACC-NO: 2000-255937
DERWENT-WEEK: 200022

TITLE: Topical treatment of sexual dysfunction, especially impotence and vaginal dryness, uses a gelled composition of a drug, e.g. papaverine, phentolamine, prostaglandin E1 or nicotinic acid

INVENTOR: DRIZEN, A; NATH, G M ; ROTHBART, P

PRIORITY-DATA: 1998US-0048335 (March 26, 1998), 1995US-0536750 (September 29, 1995), 1997US-0796578 (February 6, 1997), 1997US-0825121 (March 28, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6036977 A	March 14, 2000		009	A61K009/14

INT-CL (IPC): A61K 9/14; A61K 31/557

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 27. Document ID: EP 1107762 A1, WO 200009134 A1, AU 9951862 A

L2: Entry 27 of 33 File: DWPI Jun 20, 2001

DERWENT-ACC-NO: 2000-205887
DERWENT-WEEK: 200135

TITLE: Use of misoprostol or misoprostol acid for topical application in treatment of sexual dysfunction in women

INVENTOR: KANAKARIS, P; KAROUZAKIS, P

PRIORITY-DATA: 1998GR-0100315 (August 14, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1107762 A1	June 20, 2001	E	000	A61K031/557
WO 200009134 A1	February 24, 2000	E	013	A61K031/557
AU 9951862 A	March 6, 2000		000	A61K031/557

INT-CL (IPC): A61K 31/557

Full | Title | Citation | Front | Review | Classification | Date | Reference KWIC | Draw Desc | Image

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☐ 28. Document ID: WO 9843614 A1, AU 9865881 A, US 5952006 A, EP 971694 A1

L2: Entry 28 of 33 File: DWPI Oct 8, 1998

DERWENT-ACC-NO: 1998-542379
DERWENT-WEEK: 200022

TITLE: Treating sexual dysfunction e.g. impotency or vaginal dryness - comprises topically applying polymer matrix containing dispersed negatively charged polymer and nonionic polymer

INVENTOR: DRIZEN, A; NATH, G M ; ROTHBART, P

PRIORITY-DATA: 1997US-0825121 (March 28, 1997), 1995US-0536750 (September 29, 1995), 1997US-0796578 (February 6, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9843614 A1	October 8, 1998	E	048	A61K009/06
AU 9865881 A	October 22, 1998		000	
US 5952006 A	September 14, 1999		000	A61K009/14
EP 971694 A1	January 19, 2000	E	000	A61K009/06

INT-CL (IPC): A61K 9/06; A61K 9/14; A61K 31/557

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Image

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☐ 29. Document ID: AU 9874101 A, FR 2756283 A1, WO 9823590 A1

L2: Entry 29 of 33 File: DWPI Jun 22, 1998

DERWENT-ACC-NO: 1998-325243
DERWENT-WEEK: 199844

TITLE: New aryl piperazine amine derivatives are useful in treatment of serotonin-related disorders - e.g. depression, suicidal tendencies, panic attacks and anxiety

INVENTOR: HALAZY, S; PEREZ, M

PRIORITY-DATA: 1996FR-0014524 (November 27, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9874101 A	June 22, 1998		000	C07D213/75
FR 2756283 A1	May 29, 1998		028	C07D213/75
WO 9823590 A1	June 4, 1998	F	000	C07D213/75

INT-CL (IPC): A61K 31/44; A61K 31/495; C07D 213/75

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Clip Img | Image

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☐ 30. Document ID: RU 2169147 C2, WO 9703071 A1, AU 9665172 A, NO 9800129 A, ZA 9605921 A, EP 839145 A1, CZ 9703884 A3, SK 9800024 A3, BR 9609506 A, NZ 313164 A, US 5935973 A, JP 11508599 W, AU 708890 B, MX 9800084 A1, KR 99028918 A, HU 9901485 A2

L2: Entry 30 of 33 File: DWPI Jun 20, 2001

DERWENT-ACC-NO: 1997-132259
DERWENT-WEEK: 200144

TITLE: New naphthalene-, chroman- and benzodioxan- derivs. - bind to 5-HT1A, alpha-1 and/or alpha-2 and/or D2 receptors, used for treating CNS disorders e.g. depression, anxiety and psychoses

INVENTOR: BIRCH, A M; HEAL, D J ; KERRIGAN, F ; MARTIN, K F ; NEEDHAM, P L ; SARGENT, B J

PRIORITY-DATA: 1995GB-0014380 (July 13, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
RU 2169147 C2	June 20, 2001		000	C07D405/14
WO 9703071 A1	January 30, 1997	E	094	C07D405/14
AU 9665172 A	February 10, 1997		000	
NO 9800129 A	January 12, 1998		000	C07D405/14
ZA 9605921 A	March 25, 1998		091	A61K000/00
EP 839145 A1	May 6, 1998	E	000	
CZ 9703884 A3	June 17, 1998		000	C07D405/12
SK 9800024 A3	September 9, 1998		000	
BR 9609506 A	June 1, 1999		000	
NZ 313164 A	July 29, 1999		000	
US 5935973 A	August 10, 1999		000	A61K031/335
JP 11508599 W	July 27, 1999		104	
AU 708890 B	August 12, 1999		000	
MX 9800084 A1	March 1, 1998		000	C07D405/14
KR 99028918 A	April 15, 1999		000	C07D405/14
HU 9901485 A2	July 28, 2000		000	C07D405/14

INT-CL (IPC): A61K 0/00; A61K 31/335; A61K 31/44; A61K 31/445; A61K 31/4523; A61P 25/00; A61P 25/18; C07C 0/00; C07D 207/04; C07D 207/50; C07D 211/06; C07D 211/98; C07D 319/16; C07D 319/20; C07D 401/06; C07D 405/12; C07D 405/14; C07D 409/06; C07D 409/14; C07D 413/14; C07D 417/14

Full | Title | Citation | Front | Review | Classification | Date | Reference

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Terms	Documents
(sexual adj1 dysfunction) same topical$	33

Display 30 Documents, starting with Document: 31

Display Format: CIT Change Format

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Search Results - Record(s) 31 through 33 of 33 returned.

☐ 31. Document ID: WO 9626923 A1, AU 9649468 A, FR 2731223 A1

L2: Entry 31 of 33 File: DWPI Sep 6, 1996

DERWENT-ACC-NO: 1996-412716
DERWENT-WEEK: 199641

TITLE: New bi:tryptamine derivs. - are selective 5HT-1 receptor agonists, useful in treating e.g. migraine, anxiety or depression

INVENTOR: HALAZY, S; JOHN, G ; MARTINEZ, J ; PAUWELS, P ; PEREZ, M ; VALENTIN, J ; VALENTIN, J P

PRIORITY-DATA: 1995FR-0002425 (March 2, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9626923 A1	September 6, 1996	F	054	C07D209/16
AU 9649468 A	September 18, 1996		000	C07D209/16
FR 2731223 A1	September 6, 1996		031	C07D403/12

INT-CL (IPC): A61K 31/40; C07D 209/16; C07D 403/12; C07D 209/16; C07D 403/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw. Desc | Clip Img | Image

☐ 32. Document ID: AU 701420 B, WO 9602525 A1, FR 2722788 A1, AU 9530808 A, EP 773937 A1, JP 10502920 W, US 5789412 A, NZ 290156 A

L2: Entry 32 of 33 File: DWPI Jan 28, 1999

DERWENT-ACC-NO: 1996-105826
DERWENT-WEEK: 199916

TITLE: New aryl:piperazinyl ether(s) and amide(s) - have 5-hydroxy:tryptamine receptor antagonists properties and are useful for treating e.g. anxiety, depression, Alzheimer's disease etc.

INVENTOR: HALAZY, S; JORAND, C ; PAUWELS, P

PRIORITY-DATA: 1994FR-0008981 (July 20, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 701420 B	January 28, 1999		000	C07D295/20
WO 9602525 A1	February 1, 1996	F	097	C07D295/20
FR 2722788 A1	January 26, 1996		054	C07D403/14
AU 9530808 A	February 16, 1996		000	C07D295/20
EP 773937 A1	May 21, 1997	F	000	C07D295/20
JP 10502920 W	March 17, 1998		104	C07D213/38
US 5789412 A	August 4, 1998		000	A61K031/495
NZ 290156 A	December 23, 1998		000	C07D295/18

INT-CL (IPC): A61K 31/425; A61K 31/44; A61K 31/495; C07D 213/38; C07D 275/03; C07D 277/32; C07D 295/16; C07D 295/18; C07D 295/20; C07D 317/66; C07D 401/14; C07D 403/12; C07D 403/14; C07D 295/155; C07D 295/195; C07D 317/66; C07D 403/14; C07D 403/14; C07D 295/155; C07D 295/195; C07D 403/12; C07D 295/135; C07D 295/185; C07D 403/12 ; C07D 295/112; C07D 295/185; C07D 403/12

Full | Title | Citation | Front | Review | Classification | Date | Reference

KWIC | Draw Desc | Clip Img | Image

☐ 33. Document ID: JP 3204510 B2, WO 9422460 A1, EP 696919 A1, US 5576290 A, JP 10509130 W, US 6051555 A

L2: Entry 33 of 33 File: DWPI Sep 4, 2001

DERWENT-ACC-NO: 1994-332809
DERWENT-WEEK: 200152

TITLE: Diagnosis and treatment of male psychogenic sexual dysfunction - by administering erectogenic amt. of specified hepta- to deca-peptide amide

INVENTOR: HADLEY, M E; US5576295A,

PRIORITY-DATA: 1993US-0043159 (April 5, 1993), 1994US-0264921 (June 24, 1994), 1996US-0699571 (August 19, 1996), 1998US-0179225 (October 27, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 3204510 B2	September 4, 2001		010	A61K038/00
WO 9422460 A1	October 13, 1994	E	024	A61K037/00
EP 696919 A1	February 21, 1996	E	000	A61K037/00
US 5576290 A	November 19, 1996		008	A61K038/08
JP 10509130 W	September 8, 1998		021	A61K038/00
US 6051555 A	April 18, 2000		000	A61K038/08

INT-CL (IPC): A61K 37/00; A61K 38/00; A61K 38/08; A61K 38/12; A61K 49/00; A61P 15/10; C07K 7/00; C07K 7/06; C07K 14/685

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 6204248 B1

L5: Entry 1 of 3 File: USPT Mar 20, 2001

US-PAT-NO: 6204248
DOCUMENT-IDENTIFIER: US 6204248 B1

TITLE: Pharmaceutical preparations of glutathione and methods of administration thereof

DATE-ISSUED: March 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Demopoulos; Harry B.	Scarsdale	NY		
Seligman; Myron L.	Fairfield	CT		

US-CL-CURRENT: 514/21; 514/18

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6159500 A

L5: Entry 2 of 3 File: USPT Dec 12, 2000

US-PAT-NO: 6159500
DOCUMENT-IDENTIFIER: US 6159500 A

TITLE: Pharmaceutical preparations of glutathione and methods of administration thereof

DATE-ISSUED: December 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Demopoulos; Harry B.	Scarsdale	NY		
Seligman; Myron L.	Pleasantville	NY		

US-CL-CURRENT: 424/456; 424/451, 424/452, 424/484, 514/18, 514/474, 514/824, 514/851, 514/866, 514/879, 514/894, 514/912 , 514/913, 514/931, 514/934, 514/970

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWIC | Draw Desc | Image

☐ 3. Document ID: US 5910316 A

L5: Entry 3 of 3 File: USPT Jun 8, 1999

US-PAT-NO: 5910316
DOCUMENT-IDENTIFIER: US 5910316 A

TITLE: Use of nitric oxide-releasing agents to treat impotency

DATE-ISSUED: June 8, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Keefer; Larry K.	Bethesda	MD		
Saavedra; Joseph E.	Thurmont	MD		
Doherty; Paul C.	Cupertino	CA		
Hanamoto; Mark S.	Belmont	CA		
Place; Virgil A.	Kawaihae	HI		

US-CL-CURRENT: 424/433; 514/963, 600/38

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L7: Entry 3 of 24 File: USPT Mar 20, 2001

DOCUMENT-IDENTIFIER: US 6204248 B1
TITLE: Pharmaceutical preparations of glutathione and methods of administration thereof

BSPR:
GSH is the major antioxidant in the human body and the only one we are able to synthesize, de novo. It is also the most common small molecular weight thiol in both plants and animals. Without GSH, the immune system cannot function, and the central and peripheral nervous systems become aberrant and then cease to function. Because of the dependence on GSH as the carrier of nitric oxide, a vasodilator responsible for control of vascular tone, the cardiovascular system does not function well and eventually fails. Since all epithelial cells seem to require GSH, the intestinal lining cells don't function properly and valuable micronutrients are lost, nutrition is compromised, and microbes are given portals of entry to cause infections.

DEPR:
Coronary heart disease risk is increased by the consumption of a high-fat diet, and reduced by the intake of antioxidant vitamins, including vitamin E and vitamin C, as well as flavonoids. High fat meals impair the endothelial function through oxidative stress, resulting in impaired nitric oxide availability. It has been found that vitamin C and vitamin E restores the vasoconstriction resulting from nitric oxide production by endothelium after a high fat meal. Plotnick, G. D. et al., "Effect of Antioxidant Vitamins on the Transient Impairment of Endothelium-Dependent Brachial Artery Vasoactivity Following a Single High Fat Meal", JAMA 278: 1682-1686 (Nov. 26, 1997), incorporated herein by reference. According to the present invention, glutathione may be administered as a prophylaxis against vascular disease.

DEPR:
Different disorders generate different types of free radicals, in different environments. Therefore, different specific antioxidants are needed for these various radicals and related compounds. The commonest species and related molecules includes superoxide, .O.sub.2 --; hydroxyl, .OH; peroxy, .OOH; hydrogen peroxide, H.sub.2 O.sub.2 (splitting into hydroxyl radicals); alkoxy, RO.; delta singlet oxygen, .sup.1 O.sub.2 ; nitric oxide, .NO; lipid hydroperoxides, LOOH (splitting into alkoxy and hydroxyl radicals). See, Montaignier, Luc, Olivier, Rene, Pasquier, Catherine (Eds.), Oxidative Stress in Cancer, AIDS, and Neurodegenerative Diseases, Marcel Dekker, NY (1998), incorporated herein by reference in its entirety.

DEPR:
Glutathione need not be orally ingested in order to provide the beneficial effects noted. While the drug may be administered intravenously or parenterally, it may also be administered through mucous membranes, including sublingually, as a vaginal or rectal suppository, and by pulmonary inhaler, for topical applications to the alveolar surface cells of the lungs to enhance pulmonary protection against unusual pneumonias. Systemic administration of glutathione may be used to concentrate glutathione in lymph nodes, and lymphoid tissues.

DEPR:
The ability of glutathione to chemically dismantle the gp120 protein of HIV by chemically destroying structural disulfide bonds, indicates that transmission of

the infection may be curtailed to some extent. If gp120 is dismantled, the virus cannot lock onto CD4+ cells. The oral glutathione treatment of patients may suffice to dismantle gp120 of viruses from treated patients. The topical applications of glutathione to mucous membranes might possibly serve to protect a sex partner if unsafe sexual practices occur.

DEPR:
It is noted that the effects of various pharmacological agents which act to increase the production of nitric oxide, for example the substrate for formation of nitric oxide, the amino acid arginine, the stability of nitric oxide in the blood, or the effect of nitric oxide, may be used synergistically. Likewise, drugs which act on differing systems, such as the central nervous system and peripheral vascular system, may also be used synergistically. Thus, glutathione may be used alone or in combination to achieve its effects on the circulatory system and vascular tissues.

DEPR:
Arginine is the normal starting substrate for the production of nitric oxide. Arginine is normally in limited supply, and thus a relative deficiency of arginine may result in impaired vascular endothelial function.

DEPR:
An oral formulation is provided for prophylaxis of vascular disease. The composition includes 500 mg reduced L-glutathione, 200 mg USP grade crystalline ascorbic acid, and 200 mg arginine, in an OO-type gelatin capsule.

WEST

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L7: Entry 5 of 24 File: USPT Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6139847 A
TITLE: Combined use of angiotensin inhibitors and nitric oxide stimulators to treat fibrosis

BSPR:
One treatment approach, therefore, has been to target the early inflammatory response. Treatment with topical corticosteroids has achieved limited success, if used early in fibrosis. However, steroid therapy has little or no effect once scar tissue has already formed. Furthermore, prolonged administration of hydrocortisone, in pulmonary fibrotic disease for example, may actually worsen the condition.

BSPR:
More particularly, the combination is administered to a patient by means including pulmonary absorption, injection, topical administration, oral administration, macromolecular targeting or release from an implant.

BSPR:
The term "nitric oxide (NO) stimulator" means an agent that acts to produce increased levels of NO. Suitable agents include, but are not limited to, NO donors, NO synthase (NOS) stimulators, and NO catabolism inhibitors. Suitable NO donors include, but are not limited to, nitroglycerin, amyl nitrate, nitroprusside, isosorbide dinitrate, erythityl dinitrate, nonoates and pentaerythritol tetranitrate. Suitable NOS stimulators include, but are not limited to, bradykinin, acetylcholine, thrombin, histamine and substance P. Suitable NO catabolism inhibitors include antioxidants, such as, but not limited to, ascorbate, tocopherol and .beta.-carotene.

DEPR:
This example shows that NO profoundly affects the progression of fibrosis in the cardiovasculature. It is demonstrated that the NOS inhibitor N-nitro-L-arginine-methyl ester (L-NAME) influences the effect of AII on the cardiovasculature.

DEPR:
L-NAME was given to adult Wistar rats in drinking water (40 mg/kg/day) for between 4-40 days. Fibrosis was characterized by quantitating immuno-detectable fibronectin, the presence of inflammatory cells within interstitial and perivascular spaces and the steady state levels of mRNA for matrix genes and atrial natriuretic factor (ANF). Although blood pressure was maintained at high levels because of the lack of endogenous NO, cardiac hypertrophy or fibrosis was not observed, even after 2 weeks. If AII was given at a pressor dose after 2 weeks of L-NAME treatment, a marked fibrosis was observed that was far more severe than that seen with AII alone. However, this fibrosis did not occur if AII was administered shortly after L-NAME treatment was initiated. A sub-pressor dose of AII administered for 3 days produced only mild fibrosis. However, when administered to a rat pretreated for 2 weeks with L-NAME, the sub-pressor dose of AII caused significant fibrosis. These data indicate a counter-regulatory role for NO in modulating the AII-induced cardiac fibrosis and suggest a potentially important autocrine or paracrine role for NO in fibroblast proliferation. The table summarizes physiological parameters and densitometric data of the mRNA levels for marker genes obtained using Northern blot analyses. The groups summarized include control rats, animals given either L-NAME alone

for 17 days, angiotensin II alone for 3 days, or both drugs together, the angiotensin II being administered during the final 3 days of L-NAME treatment. Also included are drug treatments with an angiotensin II receptor antagonist (losartan) or L-arginine, a substrate for nitric oxide synthase thought to increase NO production in vivo. Blood pressure changes were most pronounced when L-NAME was given, and drug treatment did not normalize the hypertension. Heart weight/body weight ratios were increased with combined treatment of L-NAME and ang II, and this change was only partly modulated by giving either losartan or L-arginine. Fibronectin mRNA, which is an excellent index of early fibrosis, increased most dramatically in the 3-day treatment period when ang II was given to L-NAME-treated rats, the average increase being more than 50-fold that of control levels. Fibrillar collagen (Type III) also increased dramatically, and atrial natriuretic factor (ANF), a marker for myocyte hypertrophy, also was obviously affected by the combined treatment. When losartan was given at a relatively high dose of 20 mg/kg/day, there was a greater suppression of gene expression than was observed with 10/mg/kg/day, suggesting that in this model, inhibition was not accomplished at doses that would normally suppress the effects of higher amounts of angiotensin II in the absence of L-NAME treatment. Administration of L-arginine during the latter 10 days of treatment at a dose of 4 g/kg/day also markedly attenuated the response to combined treatment. Thus, both an angiotensin receptor antagonist and a potential substrate for nitric oxide synthase modulated the fibrotic response.

DETL:
TABLE 1

Effect of Drug Treatment on Blood Pressure, Heart Weight and Body Weight
Relative Change in Steady State Heart mRNA Level Systolic Weight/ Type III
Number Blood Body Collagen Treatment of Pressure Weight (fold Groups Animals (mm Hg) (.times. 1000) Fibronectin increase) ANF

Control 8 132 .+-. 2 2.86 .+-. 0.1 1 1 1 (17 days) L-NAME 6 183 .+-. 9 2.77 .+-. 0.1 1.1 .+-. 0.1 1.1 .+-. 0.1 1.0 .+-. 0.1 (17 days) Ang II 7 148 .+-. 10 3.04 .+-. 0.1 1.4 .+-. 0.2 1.2 .+-. 0.1 1.6 .+-. 0.2 (3 days) L-NAME + 10 186 .+-. 5 3.52 .+-. 0.1 55 .+-. 7.2 9.0 .+-. 1.3 14.6 .+-. 3.5 ang II L-NAME + 6 182 .+-. 7 2.80 .+-. 0.1 13.7 .+-. 5.2 6.3 .+-. 3.2 10 .+-. 7.1 ang II + losartan (10 mg/ kg/day) L-NAME + 6 169 .+-. 3 2.72 .+-. 0.1 6.8 .+-. 2.2 1.8 .+-. 1.4 1.6 .+-. 0.5 ang II + losartan (20 mg/ kg/day) L-NAME + 6 172 .+-. 7 2.74 .+-. 0.1 13.5 .+-. 3.2 1.8 .+-. 1.2 5.4 .+-. 1.1 ang II + L-arginine (4 g/kg/ day)

All data are expressed as mean .+-. standard error. All changes in steadystate mRNA levels, were expressed relative to that o control values.

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L7: Entry 6 of 24 File: USPT Oct 3, 2000

DOCUMENT-IDENTIFIER: US 6127356 A
TITLE: Oxidant scavengers

BSPR:
74:1398 (1984); Karlsson et al, Biochem. J. 255:223 (1988)). Endothelial cells secrete both O.sub.2.sup.- (Halliwell, Free Radical Res. Commun. 5:315 (1989)) and endothelium-derived relaxing factor, putatively identified as nitric oxide (NO.multidot.) (Noak and Murphy, in Oxidative Stress Oxidants and Antioxidants, eds Sies, H. (Academic, San Diego), pp. 445-489 (1991)). NO.multidot. functions as a vasoregulator and as a regulator of neurotransmission (Schuman and Madison, Science 254:1503 (1991)). NO.multidot. can, however, be toxic to neurons in some situations (Dawson et al, Proc. Natl. Acad. Sci. USA 88:6368 (1991)). O.sub.2.sup.- is known to inactivate NO.multidot. -induced vasorelaxation (Gryglewski et al, Nature 320:454 (1986); Rubanyi and Vanhoutte, Am. J. Physiol. 250:H822 (1986); Rubanyi and Vanhoutte, Am. J. Physiol. 250:H815 (1986); Bult et al, Br. J. Pharmacol. 95:1308 (1988); Nucci et al, Proc. Natl. Acad. Sci. USA 85:2334 (1988)). Thus, a possible function for EC-SOD is to protect NO.multidot. released from cells from O.sub.2.sup.- -mediated inactivation.

BSPR:
Surprisingly, it has been found that EC-SOD increases, rather than decreases, central nervous system O.sub.2 toxicity and that this effect of EC-SOD occurs through modulation of NO.multidot. This result implicates NO.multidot. as an important mediator in O.sub.2 toxicity. The invention thus relates to methods of manipulating nitric oxide function that involve the use of extracellular antioxidants.

BSPR:
The present invention relates to a method of modulating intra- or extracellular levels of oxidants such as superoxide radicals, hydrogen peroxide and peroxynitrite. More particularly, the invention relates to a method of modulating normal or pathological processes involving superoxide radicals, hydrogen peroxide, nitric oxide or peroxynitrite using low molecular weight antioxidants, for example, mimetics of SOD, catalase or peroxidase.

DRPR:
FIG. 3 shows the percent survival of transgenic and nontransgenic mice exposed to 6 ATA oxygen for 25 minutes. Mice were injected with saline or given 20 mg/kg N-.omega.-nitro-L-arginine (LNNA) i.p. 10 minutes before compression. 400 mg/kg of diethyldithiocarbamate (DDC) in saline was injected i.p. 55 min before compression. *p<0.017 tested by X.sup.2 with Bonferroni correction, compared to transgenic saline treated mice.

DRPR:
FIG. 4 shows time to onset of first seizure in transgenic and nontransgenic mice exposed to 6 ATA oxygen. Mice were injected with saline or given 20 mg/kg N-.omega.-nitro-L-arginine (LNNA) i.p. 10 minutes before beginning compression. 400 mg/kg diethyldithiocarbamate (DDC) was injected i.p. 55 minutes prior to compression. Results are expressed as mean.+-.S.D. of time to first seizure with zero time taken once chamber reached 6 ATA. *p<0.05 tested by analysis of variance with the Scheffe F-test compared to nontransgenic saline treated mice.

DRPR:

FIG. 6 shows the seizure latency in wild-type mice exposed to 6 ATA oxygen after being treated with saline or 20 mg/kg N-.omega.-nitro-L-arginine (LNNA) or 20 mg/kg N-.omega.-nitro-L-arginine plus 50 mg/kg L-arginine (LNNA+L-Arg). *p<0.05 tested by analysis of variance with a paired Student's t-test compared to saline treated mice.

DRPR:
FIG. 7 shows the percent survival in wild-type mice exposed to 6 ATA oxygen. Mice were given an i.p. injection of normal saline (0.008 cc/g) or 20 mg/kg N-.omega.-nitro-L-arginine (LNNA) (0.008 cc/g) 15 minutes prior to compression. The mice were exposed to 6 ATA of oxygen for 20 minutes (n=10, saline only), 25 minutes (n=10, both groups), 30 minutes (n=10, saline only), 50 minutes (n=6, LNNA only), 75 minutes (n=12, LNNA only), 90 minutes (n=14, LNNA only), 105 minutes (n=6 LNNA only) and 120 minutes (n=6, LNNA only) and percent survival was measured for each group.

DRPR:
FIG. 8 shows the survival dose response curve for N-.omega.-nitro-L-arginine (LNNA). Wild-type mice were given an i.p. injection of normal saline (0.008 cc/g) or 0, 2, 10, 20, or 30 mg/kg LNNA (0.008 cc/g) 15 minutes prior to compression and then exposed to 75 minutes at 6 ATA oxygen. Percent survival was calculated for each treatment group.

DRPR:
FIG. 9 shows the percent survival in wild-type mice pretreated with saline, 20 mg/kg N-.omega.-nitro-L-arginine (LNNA), or 20 mg/kg N-.omega.-nitro-L-arginine plus 50 mg/kg L-arginine (LNNA+L-Arg) and then exposed to 75 minutes of 6 ATA oxygen. *p<0.05 tested with a X-square test with Bonferroni correction.

DRPR:
FIG. 10 shows the percent survival in transgenic and nontransgenic mice exposed to 6 ATA oxygen for 75 minutes. Mice were injected with saline or given 20 mg/kg N-.omega.-nitro-L-arginine (LNNA) i.p. 10 minutes before compression. *p<0.05 tested by X.sup.2 compared to nontransgenic saline treated mice. .dagger.p<0.05 tested by X.sup.2 compared to transgenic saline treated mice.

DEPR:
The present invention relates to methods of protecting against the deleterious effects of oxidants, particularly, superoxide radicals, hydrogen peroxide and peroxynitrite, and to methods of preventing and treating disease states that involve or result from oxidant stress. The invention also relates methods of modulating biological processes involving oxidants, including superoxide radicals, hydrogen peroxide, nitric oxide and peroxynitrite. The invention further relates to compounds and compositions, including low molecular weight antioxidants (eg mimetics of scavengers of reactive oxygen species, including mimetics of SODs, catalases and peroxidases) and formulations thereof, suitable for use in such methods.

DEPR:
The polypeptides and mimetics described above can be formulated into pharmaceutical compositions suitable for use in the present methods. Such compositions include the active agent (polypeptide or mimetic) together with a pharmaceutically acceptable carrier, excipient or diluent. The composition can be present in dosage unit form for example, tablets, capsules or suppositories. The composition can also be in the form of a sterile solution suitable for injection or nebulization. Compositions can also be in a form suitable for opthalmic use. The invention also includes compositions formulated for topical administration, such compositions taking the form, for example, of a lotion, cream, gel or ointment. The concentration of active agent to be included in the composition can be selected based on the nature of the agent, the dosage regimen and the result sought.

DEPR:
The dosage of the composition of the invention to be administered can be determined without undue experimentation and will be dependent upon various

factors including the nature of the active agent, the route of administration, the patient, and the result sought to be achieved. A suitable dosage of protein administered IV can be expected to be in the range of about 10-1000 mg/day. For topical treatment, it is expected that lower doses will be required (see WO 91/04315); for aerosol administration, it is expected that doses will be in the range of 1 to 10 mg/kg. Suitable doses of mimetics will vary, for example, with the mimetic and with the result sought. The results of Faulkner et al (J. Biol. Chem. 269:23471 (1994)) indicate that the in vivo oxidoreductase activity of the mimetics is such that a pharmaceutically effective dose will be low enough to avoid problems of toxicity. Doses that can be used include those in the range of 1 to 50 mg/kg.

DEPR:
Treatment with N-.omega.-nitro-L-arginine, an inhibitor of nitric oxide synthase: Ten minutes prior to beginning compression, 0.008 cc/g saline or 20 mg/kg (0.008 cc/g) N-.omega.-nitro-L-arginine dissolved in sterile water was given i.p to the transgenic and nontransgenic mice. Mice were then exposed at 6 ATA oxygen for 25 or 75 minutes as described above.

DEPR:
One possibility that might explain why EC-SOD exacerbates CNS oxygen toxicity would be that nitric oxide is a mediator of CNS oxygen toxicity and EC-SOD is protecting nitric oxide from superoxide mediated inactivation. To test the hypothesis that nitric oxide contributes to CNS oxygen toxicity, wild-type (C57BL/6 X C3H)F1 mice were treated with an inhibitor of nitric oxide synthase, N-.omega.-nitro-L-arginine. FIG. 6 shows the effects of N-.omega.-nitro-L-arginine on seizure latency in mice. Pretreatment with N-.omega.-nitro-L-arginine resulted in a significant increase in seizure latency (13.50.+-.5.6 min) when compared to saline treated mice (2.75.+-.1 min). FIG. 7 shows that nitric oxide synthase inhibition also significantly increased survival after exposure to hyperbaric oxygen. Mice given the inhibitor of nitric oxide synthase displayed 50% mortality after exposure to 90 minutes of 6 ATA oxygen and 100% mortality was not obtained until after 2 hours of this exposure. Saline treated mice, however, had a 50% mortality after only 25 minutes of exposure, with 100% mortality after only 30 minutes at 6 ATA of oxygen. FIG. 8 shows that the percent survival in hyperbaric oxygen was dependent on the dose of the inhibitor given. The protection offered by this competitive inhibitor of nitric oxide synthase could be reversed when an excess of L-arginine was given (FIG. 6 and FIG. 9).

DEPR:
The effects of the nitric oxide synthase inhibitor, N-.omega.-nitro-L-arginine, upon CNS oxygen toxicity was then studied in the transgenic mice. This treatment dramatically reduced CNS oxygen toxicity in both transgenic and nontransgenic mice. Survival after a 25 minute exposure to 6 ATA oxygen increased to 100% in both groups (FIG. 3). Seizure latency was also significantly delayed (FIG. 4). The exposure time was then increased to 75 minutes to investigate whether transgenic mice were still more sensitive than nontransgenic mice to hyperbaric oxygen. The results in FIG. 10 indicate that treatment with N-.omega.-nitro-L-arginine abolished the difference in sensitivity that was observed between untreated transgenic and nontransgenic mice during the 25 minute exposure shown in FIG. 3.

DEPR:
Chemical treatments: Six groups of experiments were conducted to investigate the importance of extracellular superoxide, iron, and nitric oxide in cold-induced brain edema. In all groups, drugs were dissolved in saline and injected at 0.008 cc/g 15 minutes prior to cold injury. In Group 1, edema formation of EC-SOD transgenic mice was compared with that of nontransgenic littermates. Group 2 compared edema formation between wild-type (C57BL/6 X C3H)F1 mice treated with saline and (C57BL/6 X C3H)F1 mice treated with 0.33 mg/g deferoxamine (0.51 .mu.moles/g). Group 3 compared (C57BL/6 X C3H)F1 mice treated with saline to (C57BL/6 X C3H)F1 mice treated with 0.51 .mu.moles/g Fe.sup.3+ -saturated deferoxamine. Group 4 consisted of (C57BL/6 X C3H)F1 mice treated with saline and (C57BL/6 X C3H)F1 mice treated with 0.02 mg/g N-.omega.-nitro-L-arginine

methyl ester. Group 5 consisted of (C57BL/6 X C3H)F1 mice treated with saline and (C57EL/6 X C3H)F1 mice treated with 0.02 mg/g N-.omega.-nitro-L-arginine methyl ester plus 0.05 mg/g L-arginine. Group 6 compared edema formation between nontransgenic mice, EC-SOD transgenic mice treated with saline, and EC-SOD transgenic mice treated with 0.02 mg/g N-.omega.-nitro-L-arginine methyl ester.

DEPR:
To test this hypothesis, the synthesis of nitric oxide was inhibited with N-.omega.-nitro-L-arginine methyl ester, a competitive inhibitor of the enzyme nitric oxide synthase, to determine if this would result in protection against edema formation after a cold-induced injury. Table III shows that treatment with N-.omega.-nitro-L-arginine methyl ester significantly protected mice against edema formation resulting in 37% less edema formation than that occurring in saline treated controls. This protection by N-.omega.-nitro-L-arginine methyl ester was reversed by simultaneous administration of an excess of L-arginine to the mice (Table III).

DEPR:
In the final experiments, EC-SOD transgenic mice were treated with either saline or N-.omega.-nitro-L-arginine methyl ester to determine if there was an additive effect in preventing edema formation in mice which have both increased levels of EC-SOD as well as the inhibitor of nitric oxide synthase. Table IV shows that when EC-SOD transgenic mice were given the inhibitor of nitric oxide synthase, no added protection against edema formation was detected relative to transgenic mice protected only by increased levels of EC-SOD in the brain.

DEPR:
To determine whether addition of MnTBAP after initiation of the excitotoxic insult exerted neuroprotective effects, 100 .mu.M NMDA was included for 15 min. in HBSS+(Ca.sup.++ -, Mg++-free HBSS containing 5.6 mM glucose and supplemented with 2 mM CaCl.sub.2, 1 mM NaHCO.sub.3, 10 mM HEPES and 5 .mu.M glycine). This acute exposure paradigm induced delayed neuronal death (measured 18 hr. later) and allowed determination of the temporal relationship between MnTBAP exposure and neuroprotection. The neuroprotective effects of MnTBAP were assessed when it was: 1) present 15 min. prior to and during a 15 min. NMDA application (but not for the 18 hr. period after media change) (condition "pre"); 2) present 15 min. prior to and during a 15 min. NMDA application and for the ensuing 18 hr. (condition "pre+post"); 3) added 15, 30 or 60 min. following a 15 min. incubation with 100 .mu.M NMDA and left in the media for the ensuing 18 hr. Condition "pre" resulted in a 25% reduction of LDH release measured 18 hr. later; using an identical time course of application of 100 .mu.M D-APV in condition "pre", a complete blockade of LDH release was observed. In contrast, MnTBAP incubated as in condition "pre+post" resulted in a 51% reduction of LDH release. Addition of 200 .mu.M MnTBAP 15, 30 or 60 min. following a 15 min. exposure to 100 .mu.M NMDA resulted in a 38%, 30% and 25% reduction of LDH release respectively. In contrast, addition of 10 .mu.M MK801 15 min. after NMDA treatment had a modest protective effect (17%) when added 15 min. after the NMDA insult. In order to investigate the possibility that NMDA-induced aconitase inactivation resulted from peroxynitrite formation, the effects of nitric oxide synthase (NOS) inhibitors on NMDA-induced aconitase inactivation and cell death were examined. NMDA-induced aconitase inactivation and LDH release were unchanged by the presence of 1 mM of either N.sup.G -nitro-L-arginine methyl ester, N.sup.G -nitro-L-arginine or N.sup.G -monomethyl-L-arginine. NOS, however, was expressed in the cortical neuronal preparation used. Thus, peroxynitrite would not appear to play an etiological role in NMDA-induced aconitase inactivation or cell death under the conditions used.

DEPR:
MnTBAP caused a dose-dependent inhibition of nitrite/nitrate production in cells stimulated with LPS. However, in cells immunostimulated with the combination of LPS and IFN, MnTBAP caused a less pronounced inhibition of nitrite, nitrate accumulation (300 .mu.M). For instance, at 100 .mu.M and 300 .mu.M, MnTBAP caused a significant, 63 and 86% inhibition, of the LPS-induced nitrite/nitrate accumulation. When given in the combined presence of LPS and IFN, 100 .mu.M MnTBAP only caused a 25% inhibition of nitrite/nitrate accumulation and

pronounced inhibition (61%) was only observed at the highest concentration of MnTBAP tested (300 .mu.M). L-NMA (N.sup.G -methyl-L-arginine) caused a near-complete inhibition of the production of NO in cells stimulated with LPS or LPS and IFN; and MnTBAP had no additional effect on nitrite/nitrate formation in the presence of L-NMA. The inhibition of nitrite/nitrate accumulation by MnTBAP in LPS-stimulated macrophages diminished by more than 50% when the agent was applied 6 h after LPS, whereas in the case of the inhibition seen with L-NMA, the extent of inhibition seen was similar when the compound was given together with LPS or at 6 h thereafter (n=6).

DETL:
TABLE III The effect of inhibition of nitric oxide synthesis on edema formation after cold-induced brain injury. Wild-type (C57BL/6 .times. C3H)F1 mice were treated with the competitive inhibitor of nitric oxide synthase, N-.omega.- nitro-L-arginine methyl ester (LNAME) to determine what effect nitric oxide had on vasogenic edema. Mice were also given N-.omega.-nitro-L-arginine methyl ester plus an excess of L-arginine (LNAME + L-Arg) to see if the effects seen with LNAME alone could be reversed. Values are presented as mean .+-. standard error. Treatment n Edema Index Saline 6 5.77 .+-. 0.29 LNAME 6 3.65 .+-. 0.51* Saline 6 6.56 .+-. 0.21 LNAME + L-Arg 6 6.03 .+-. 0.71 *p < 0.05 compared to Edema Index of respective saline treated controls using a paired Student's ttest.

DETL:
TABLE IV Evaluation of the effect of inhibition of nitric oxide synthesis on edema formation in transgenic mice. Comparison of edema formation in nontransgenic mice to edema formation in transgenic mice with elevated levels of brain EC-SOD activity, and to edema formation in transgenic mice treated with an inhibitor of nitric oxide synthesis (20 mg/kg N-.omega.-nitro-L-arginine; Transgenic + LNAME) 15 minutes prior to cold-induced injury. Values are presented as mean .+-. standard error and were compared using analysis of variance with a Fisher PLSD test. No significant difference was seen between transgenic and transgenic .+-. LNAME mice. Treatment n Edema Index Nontransgenic 6 7.91 .+-. 0.67 Transgenic 6 4.91 .+-. 0.78* Transgenic + LNAME 6 4.30 .+-. 0.96* *p < 0.05 compared to Edema Index of nontransgenic mice.